

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (withdrawn) A variant Hepatitis B Virus (HBV) comprising a surface component exhibiting an altered immunological profile compared to a reference HBV.
2. (withdrawn) A variant HBV according to claim 1 wherein the surface component on the variant is a surface antigen which comprises a single or multiple amino acid substitution, addition and/or deletion or truncation compared to a surface antigen from said reference HBV and wherein an antibody generated to the reference surface antigen from the reference HBV exhibits reduced capacity for neutralizing said variant HBV.
3. (withdrawn) A variant HBV according to claim 2 wherein the surface antigen on the variant comprises an amino acid substitution, addition and/or deletion or truncation compared to the amino acid sequence set forth below:

M X₁ X₂ X₃ X₄ S G X₅ L X₆ P L X₇ V L Q A X₈ X₉ F X₁₀ L T X₁₁ I X₁₂ X₁₃ I P X₁₄ S L X₁₅ S W W
T S L N F L G X₁₆ X₁₇ X₁₈ X₁₉ C X₂₀ G X₂₁ N X₂₂ Q S X₂₃ X₂₄ S X₂₅ H X₂₆ P X₂₇ X₂₈ C P P X₂₉ C
X₃₀ G Y R W M C L X₃₁ R F I I F L X₃₂ I L L L C L I F L L V L L D X₃₃ Q G M L X₃₄ V C P L
X₃₅ P X₃₆ X₃₇ X₃₈ T T S X₃₉ X₄₀ X₄₁ C X₄₂ T C X₄₃ X₄₄ X₄₅ X₄₆ Q G X₄₇ S X₄₈ X₄₉ P X₅₀ X₅₁ C C
X₅₂ K P X₅₃ X₅₄ G N C T C I P I P S X₅₅ W A X₅₆ X₅₇ X₅₈ X₅₉ L W E X₆₀ X₆₁ S X₆₂ R X₆₃ S W L
X₆₄ L L X₆₅ X₆₆ F V Q X₆₇ X₆₈ X₆₉ X₇₀ L X₇₁ P X₇₂ V W X₇₃ X₇₄ X₇₅ I W X₇₆ X₇₇ W X₇₈ W X₇₉ P
X₈₀ X₈₁ X₈₂ X₈₃ I X₈₄ X₈₅ P F X₈₆ P L L P I F X₈₇ X₈₈ L X₈₉ X₉₀ X₉₁ I [Formula I];

wherein:

X₁ is E or G or D;

X₂ is N or S or K;

X₃ is I or T;
X₄ is T or A;
X₅ is F or L;
X₆ is G or R;
X₇ is L or R;
X₈ is G or V;
X₉ is F or C;
X₁₀ is L or S or W;
X₁₁ is R or K;
X₁₂ is L or R;
X₁₃ is T or K;
X₁₄ is Q or K;
X₁₅ is D or H;
X₁₆ is G or E or A;
X₁₇ is S or A or V or T or L;
X₁₈ is P or T;
X₁₉ is V or R or T or K or G;
X₂₀ is L or P;
X₂₁ is Q or L or K;
X₂₂ is S or L;
X₂₃ is P or Q;
X₂₄ is T or I;
X₂₅ is N or S;
X₂₆ is S or L;

X₂₇ is T or I;
X₂₈ is S or C;
X₂₉ is I or T;
X₃₀ is P or A;
X₃₁ is R or Q;
X₃₂ is F or C;
X₃₃ is Y or C;
X₃₄ is P or H or S;
X₃₅ is I or L;
X₃₆ is G or R;
X₃₇ is S or T;
X₃₈ is T or S;
X₃₉ is T or V or A;
X₄₀ is G or E or Q;
X₄₁ is P or A or S;
X₄₂ is K or R;
X₄₃ is T or M;
X₄₄ is T or I or S or A;
X₄₅ is P or T or A or I or L;
X₄₆ is A or V;
X₄₇ is N or T;
X₄₈ is M or K or L;
X₄₉ is F or Y or I;
X₅₀ is S or Y;

X₅₁ is C or S;
X₅₂ is T or I or S;
X₅₃ is T or S;
X₅₄ is D or A;
X₅₅ is S or T;
X₅₆ is F or L;
X₅₇ is A or G or V;
X₅₈ is K or R or T;
X₅₉ is Y or F;
X₆₀ is W or G;
X₆₁ is A or G;
X₆₂ is V or A;
X₆₃ is F or L;
X₆₄ is S or N;
X₆₅ is V or A;
X₆₆ is P or Q;
X₆₇ is W or C or S;
X₆₈ is F or C;
X₆₉ is V or D or A;
X₇₀ is G or E;
X₇₁ is S or F;
X₇₂ is T or I;
X₇₃ is L or P;
X₇₄ is S or L;

X₇₅ is A or V;
X₇₆ is M or I;
X₇₇ is M or I;
X₇₈ is Y or F;
X₇₉ is G or E;
X₈₀ is S or N or K;
X₈₁ is L or Q;
X₈₂ is Y or F or H or C;
X₈₃ is S or G or N or D or T;
X₈₄ is V or L;
X₈₅ is S or N;
X₈₆ is I or M or L;
X₈₇ is F or C;
X₈₈ is C or Y;
X₈₉ is W or R;
X₉₀ is V or A; and
X₉₁ is Y or I or S;

and wherein the variant HBV is selected for by a nucleotide analogue of HBV DNA polymerase.

4. (withdrawn) A variant HBV according to claim 2 wherein the surface antigen on the variant comprises an amino acid substitution, addition and/or deletion or truncation compared to the amino acid sequence set forth below:

$M X_1 X_2 X_3 X_4 S G X_5 L X_6 P L X_7 V L Q A X_8 X_9 F X_{10} L T X_{11} I X_{12} X_{13} I P X_{14} S L X_{15} S W W$
 $T S L N F L G X_{16} X_{17} X_{18} X_{19} C X_{20} G X_{21} N X_{22} Q S X_{23} X_{24} S X_{25} H X_{26} P X_{27} X_{28} C P P X_{29} C$
 $X_{30} G Y R W M C L X_{31} R F I I F L X_{32} I L L L C L I F L L V L L D X_{33} Q G M L X_{34} V C P L$
 $X_{35} P X_{36} X_{37} X_{38} T T S X_{39} X_{40} X_{41} C X_{42} T C X_{43} X_{44} X_{45} X_{46} Q G X_{47} S X_{48} X_{49} P X_{50} X_{51} C C$
 $X_{52} K P X_{53} X_{54} G N C T C I P I P S X_{55} W A X_{56} X_{57} X_{58} X_{59} L W E X_{60} X_{61} S X_{62} R X_{63} S W L$
 $X_{64} L L X_{65} X_{66} F V Q X_{67} X_{68} X_{69} X_{70} L X_{71} P X_{72} V W X_{73} X_{74} X_{75} I W X_{76} X_{77} W X_{78} W X_{79} P$
 $X_{80} X_{81} X_{82} X_{83} I X_{84} X_{85} P F X_{86} P L L P I F X_{87} X_{88} L X_{89} X_{90} X_{91} I [Formula I];$

wherein:

X_1 is E or G or D;

X_2 is N or S or K;

X_3 is I or T;

X_4 is T or A;

X_5 is F or L;

X_6 is G or R;

X_7 is L or R;

X_8 is G or V;

X_9 is F or C;

X_{10} is L or S or W;

X_{11} is R or K;

X_{12} is L or R;

X_{13} is T or K;

X_{14} is Q or K;

X_{15} is D or H;

X_{16} is G or E or A;

X₁₇ is S or A or V or T or L;

X₁₈ is P or T;

X₁₉ is V or R or T or K or G;

X₂₀ is L or P;

X₂₁ is Q or L or K;

X₂₂ is S or L;

X₂₃ is P or Q;

X₂₄ is T or I;

X₂₅ is N or S;

X₂₆ is S or L;

X₂₇ is T or I;

X₂₈ is S or C;

X₂₉ is I or T;

X₃₀ is P or A;

X₃₁ is R or Q;

X₃₂ is F or C;

X₃₃ is Y or C;

X₃₄ is P or H or S;

X₃₅ is I or L;

X₃₆ is G or R;

X₃₇ is S or T;

X₃₈ is T or S;

X₃₉ is T or V or A;

X₄₀ is G or E or Q;

X₄₁ is P or A or S;
X₄₂ is K or R;
X₄₃ is T or M;
X₄₄ is T or I or S or A;
X₄₅ is P or T or A or I or L;
X₄₆ is A or V;
X₄₇ is N or T;
X₄₈ is M or K or L;
X₄₉ is F or Y or I;
X₅₀ is S or Y;
X₅₁ is C or S;
X₅₂ is T or I or S;
X₅₃ is T or S;
X₅₄ is D or A;
X₅₅ is S or T;
X₅₆ is F or L;
X₅₇ is A or G or V;
X₅₈ is K or R or T;
X₅₉ is Y or F;
X₆₀ is W or G;
X₆₁ is A or G;
X₆₂ is V or A;
X₆₃ is F or L;
X₆₄ is S or N;

X₆₅ is V or A;
X₆₆ is P or Q;
X₆₇ is W or C or S;
X₆₈ is F or C;
X₆₉ is V or D or A;
X₇₀ is G or E;
X₇₁ is S or F;
X₇₂ is T or I;
X₇₃ is L or P;
X₇₄ is S or L;
X₇₅ is A or V;
X₇₆ is M or I;
X₇₇ is M or I;
X₇₈ is Y or F;
X₇₉ is G or E;
X₈₀ is S or N or K;
X₈₁ is L or Q;
X₈₂ is Y or F or H or C;
X₈₃ is S or G or N or D or T;
X₈₄ is V or L;
X₈₅ is S or N;
X₈₆ is I or M or L;
X₈₇ is F or C;
X₈₈ is C or Y;

X₈₉ is W or R;

X₉₀ is V or A; and

X₉₁ is Y or I or S.

and wherein the variant HBV is selected for following immunological therapy directed against a surface antigen as defined in Formula I.

5. (withdrawn) A variant HBV according to claim 1 comprising a nucleotide sequence having a single or multiple nucleotide substitution, addition and/or deletion or truncation of the nucleotide sequence as set forth in formula III below:

ACN₁AAACCTN₂N₃GGAN₄GGAAAN₅TGCACN₆TGTATTCCCATCC
CATCN₇TCN₈TGGGCTTTCGN₉AAAN₁₀ATN₁₁CCTATGGGAGN₁₂GGG
CCTCAGN₁₃CCGTTTCTCN₁₄TGGCTCAGTTTACTAGTGCCATTT
GTTTCAGTGGTTCGN₁₅AGGGCTTTCCCCCACTGTN₁₆TGGCTTTC
AGN₁₇TATATGGATGATGTGGTN₁₈TTGGGGGGCCAAGTCTGTAC
AN₁₉CATCN₂₀TGAGTCCCTTTN₂₁TN₂₂CCN₂₃CTN₂₄TTACCAATTTT
CTTN₂₅TGTCTN₂₆TGGGN₂₇ATACATT [Formula III];

wherein:

N₁ is A or C;

N₂ is T or A;

N₃ is C or T;

N₄ is C or T;

N₅ is C or T;

N₆ is C or T;
N₇ is A or G;
N₈ is T or C;
N₉ is C or G;
N₁₀ is G or A;
N₁₁ is T or A;
N₁₂ is T or G;
N₁₃ is T or C;
N₁₄ is C or T;
N₁₅ is T or C;
N₁₆ is T or C;
N₁₇ is T or C;
N₁₈ is A or T;
N₁₉ is A or G;
N₂₀ is T or G;
N₂₁ is A or T;
N₂₂ is A or G;
N₂₃ is T or G;
N₂₄ is A or G;
N₂₅ is T or C;
N₂₆ is T or C; and
N₂₇ is T or C.

and wherein the HBV variant has a surface antigen exhibiting an altered immunological profile relative to the surface antigen as defined in Formula I.

6. (withdrawn) An isolated variant Hepatitis B virus surface antigen (HBsAg) or a recombinant form thereof or a derivative or chemical equivalent thereof wherein said HBsAg or its recombinant or derivative form or its chemical equivalent exhibits an altered immunological profile compared to an HBsAg from a reference HBV.

7. (withdrawn) An isolated variant HBsAg or a recombinant or derivative form thereof or a chemical equivalent thereof according to claim 6 wherein the variant HBsAg comprises an amino acid sequence having a single or multiple substitution, addition and/or deletion or truncation of the amino acid sequence set forth below:

M X₁ X₂ X₃ X₄ S G X₅ L X₆ P L X₇ V L Q A X₈ X₉ F X₁₀ L T X₁₁ I X₁₂ X₁₃ I P X₁₄ S L X₁₅ S W W
T S L N F L G X₁₆ X₁₇ X₁₈ X₁₉ C X₂₀ G X₂₁ N X₂₂ Q S X₂₃ X₂₄ S X₂₅ H X₂₆ P X₂₇ X₂₈ C P P X₂₉ C
X₃₀ G Y R W M C L X₃₁ R F I I F L X₃₂ I L L L C L I F L L V L L D X₃₃ Q G M L X₃₄ V C P L
X₃₅ P X₃₆ X₃₇ X₃₈ T T S X₃₉ X₄₀ X₄₁ C X₄₂ T C X₄₃ X₄₄ X₄₅ X₄₆ Q G X₄₇ S X₄₈ X₄₉ P X₅₀ X₅₁ C C
X₅₂ K P X₅₃ X₅₄ G N C T C I P I P S X₅₅ W A X₅₆ X₅₇ X₅₈ X₅₉ L W E X₆₀ X₆₁ S X₆₂ R X₆₃ S W
L X₆₄ L L X₆₅ X₆₆ F V Q X₆₇ X₆₈ X₆₉ X₇₀ L X₇₁ P X₇₂ V W X₇₃ X₇₄ X₇₅ I W X₇₆ X₇₇ W X₇₈ W
X₇₉ P X₈₀ X₈₁ X₈₂ X₈₃ I X₈₄ X₈₅ P F X₈₆ P L L P I F X₈₇ X₈₈ L X₈₉ X₉₀ X₉₁ I [Formula I];

wherein:

X₁ is E or G or D;

X₂ is N or S or K;

X₃ is I or T;

X₄ is T or A;

X₅ is F or L;

X₆ is G or R;
X₇ is L or R;
X₈ is G or V;
X₉ is F or C;
X₁₀ is L or S or W;
X₁₁ is R or K;
X₁₂ is L or R;
X₁₃ is T or K;
X₁₄ is Q or K;
X₁₅ is D or H;
X₁₆ is G or E or A;
X₁₇ is S or A or V or T or L;
X₁₈ is P or T;
X₁₉ is V or R or T or K or G;
X₂₀ is L or P;
X₂₁ is Q or L or K;
X₂₂ is S or L;
X₂₃ is P or Q;
X₂₄ is T or I;
X₂₅ is N or S;
X₂₆ is S or L;
X₂₇ is T or I;
X₂₈ is S or C;
X₂₉ is I or T;

X₃₀ is P or A;
X₃₁ is R or Q;
X₃₂ is F or C;
X₃₃ is Y or C;
X₃₄ is P or H or S;
X₃₅ is I or L;
X₃₆ is G or R;
X₃₇ is S or T;
X₃₈ is T or S;
X₃₉ is T or V or A;
X₄₀ is G or E or Q;
X₄₁ is P or A or S;
X₄₂ is K or R;
X₄₃ is T or M;
X₄₄ is T or I or S or A;
X₄₅ is P or T or A or I or L;
X₄₆ is A or V;
X₄₇ is N or T;
X₄₈ is M or K or L;
X₄₉ is F or Y or I;
X₅₀ is S or Y;
X₅₁ is C or S;
X₅₂ is T or I or S;
X₅₃ is T or S;

X₅₄ is D or A;
X₅₅ is S or T;
X₅₆ is F or L;
X₅₇ is A or G or V;
X₅₈ is K or R or T;
X₅₉ is Y or F;
X₆₀ is W or G;
X₆₁ is A or G;
X₆₂ is V or A;
X₆₃ is F or L;
X₆₄ is S or N;
X₆₅ is V or A;
X₆₆ is P or Q;
X₆₇ is W or C or S;
X₆₈ is F or C;
X₆₉ is V or D or A;
X₇₀ is G or E;
X₇₁ is S or F;
X₇₂ is T or I;
X₇₃ is L or P;
X₇₄ is S or L;
X₇₅ is A or V;
X₇₆ is M or I';
X₇₇ is M or I;

X₇₈ is Y or F;
X₇₉ is G or E;
X₈₀ is S or N or K;
X₈₁ is L or Q;
X₈₂ is Y or F or H or C;
X₈₃ is S or G or N or D or T;
X₈₄ is V or L;
X₈₅ is S or N;
X₈₆ is I or M or L;
X₈₇ is F or C;
X₈₈ is C or Y;
X₈₉ is W or R;
X₉₀ is V or A; and
X₉₁ is Y or I or S;

and wherein a neutralizing antibody directed to a reference HBV exhibits no or reduced neutralizing activity to an HBV carrying said variant HBsAg.

8. (withdrawn) An isolated variant HBsAg according to claim 7 encoded by a nucleotide sequence having a single or multiple nucleotide substitution, addition and/or deletion or truncation relative to the nucleotide sequence set forth below:

ACN₁AAACCTN₂N₃GGAN₄GGAAAN₅TGCACN₆TGTATTCCCATCC
CATCN₇TCN₈TGGGCTTTCGN₉AAAN₁₀ATN₁₁CCTATGGGAGN₁₂GGG
CCTCAGN₁₃CCGTTTCTCN₁₄TGGCTCAGTTTACTAGTGCCATTT

G T T C A G T G G T T C G N₁₅ A G G G C T T T C C C C C A C T G T N₁₆ T G G C T T T C
A G N₁₇ T A T A T G G A T G A T G T G G T N₁₈ T T G G G G G C C A A G T C T G T A C
A N₁₉ C A T C N₂₀ T G A G T C C C T T T N₂₁ T N₂₂ C C N₂₃ C T N₂₄ T T A C C A A T T T T
C T T N₂₅ T G T C T N₂₆ T G G G N₂₇ A T A C A T T [FORMULA III];

wherein:

- N₁ is A or C;
- N₂ is T or A;
- N₃ is C or T;
- N₄ is C or T;
- N₅ is C or T;
- N₆ is C or T;
- N₇ is A or G;
- N₈ is T or C;
- N₉ is C or G;
- N₁₀ is G or A;
- N₁₁ is T or A;
- N₁₂ is T or G;
- N₁₃ is T or C;
- N₁₄ is C or T;
- N₁₅ is T or C;
- N₁₆ is T or C;
- N₁₇ is T or C;
- N₁₈ is A or T;

N₁₉ is A or G;
N₂₀ is T or G;
N₂₁ is A or T;
N₂₂ is A or G;
N₂₃ is T or G;
N₂₄ is A or G;
N₂₅ is T or C;
N₂₆ is T or C; and
N₂₇ is T or C.

9. (withdrawn) A variant HBV or an isolated HBsAg from said variant HBV wherein said variant HBV comprises an HBsAg having a single or multiple amino acid substitution, addition and/or deletion or truncation relative to the HBsAg on a reference HBV and whereas the HBsAg variant is defined by a single or multiple amino acid substitution, addition and/or truncation to the catalytic region of HBV DNA polymerase as defined below:

S Z₁ L S W L S L D V S A A F Y H Z₂ P L H P A A M P H L L Z₃ G S S G L Z₄ R Y V A R L S
S Z₅ S Z₆ Z₇ X N Z₈ Q Z₉ Z₁₀ X X X Z₁₁ L H Z₁₂ Z₁₃ C S R Z₁₄ L Y V S L Z₁₅ L L Y Z₁₆ T Z₁₇ G
Z₁₈ K L H L Z₁₉ Z₂₀ H P I Z₂₁ L G F R K Z₂₂ P M G Z₂₃ G L S P F L L A Q F T S A I Z₂₄ Z₂₅ Z₂₆
Z₂₇ Z₂₈ R A F Z₂₉ H C Z₃₀ Z₃₁ F Z₃₂ Y M * D D Z₃₃ V L G A Z₃₄ Z₃₅ Z₃₆ Z₃₇ H Z₃₈ E Z₃₉ L Z₄₀ Z₄₁
Z₄₂ Z₄₃ Z₄₄ Z₄₅ Z₄₆ L L Z₄₇ Z₄₈ G I H L N P Z₄₉ K T K R W G Y S L N F M G Y Z₅₀ I G [Formula
II];

wherein:

X is any amino acid;
Z₁ is N or D;

Z₂ is I or P;
Z₃ is I or V;
Z₄ is S or D;
Z₅ is T or N;
Z₆ is R or N;
Z₇ is N or I;
Z₈ is N or Y or H;
Z₉ is H or Y;
Z₁₀ is G or R;
Z₁₁ is D or N;
Z₁₂ is D or N;
Z₁₃ is S or Y;
Z₁₄ is N or Q;
Z₁₅ is L or M;
Z₁₆ is K or Q;
Z₁₇ is Y or F;
Z₁₈ is R or W;
Z₁₉ is Y or L;
Z₂₀ is S or A;
Z₂₁ is I or V;
Z₂₂ is I or L;
Z₂₃ is V or G;
Z₂₄ is C or L;
Z₂₅ is A or S;

Z₂₆ is V or M;
Z₂₇ is V or T;
Z₂₈ is R or C;
Z₂₉ is F or P;
Z₃₀ is L or V;
Z₃₁ is A or V;
Z₃₂ is S or A;
Z₃₃ is V or L or M;
Z₃₄ is K or R;
Z₃₅ is S or T;
Z₃₆ is V or G;
Z₃₇ is Q or E;
Z₃₈ is L or S or R;
Z₃₉ is S or F;
Z₄₀ is F or Y;
Z₄₁ is T or A;
Z₄₂ is A or S;
Z₄₃ is V or I;
Z₄₄ is T or C;
Z₄₅ is N or S;
Z₄₆ is F or V;
Z₄₇ is S or D;
Z₄₈ is L or V;
Z₄₉ is N or Q;

Z₅₀ is V or I; and

M* is amino acid 550.

10. (currently amended) A variant ~~HBV or variant HBsAg from said variant HBV~~ comprising a the mutation selected from the list consisting of G112R, T123P, Y/F134S, D144E, G145R, A157D, E164D, F170L, M195I, W196L, S196W, W196STOP, M198I, W199S, S204T and S210R wherein "STOP" means a stop codon.

11. (withdrawn) A variant HBV or variant HBsAg from said variant HBV comprising a mutation selected from the list consisting of:
D144E, G145R, A157D, E164D, M195I, W196L, S196W, W196STOP, M198I, W199S and S210R wherein "STOP" means a codon.

12. (withdrawn) A variant HBV or variant HBsAg from said variant HBV comprising a mutation selected from the list consisting of:
Q476, N480G, N485K, K495R, R499O, G499E, W499Q, F512L, I515L, V519L, L526M, M550V, M550I, V553I and S565P.

13. (currently amended) A composition comprising ~~a variant HBV or~~ the variant HBsAg according to ~~any one of claims 1 to 12~~ claim 10 and one or more pharmaceutically acceptable carriers and/or diluents.

14. (canceled).

15. (withdrawn) A method for the treatment or prophylaxis of HBV infection said method comprising administering to a subject an amount of a variant HBV or variant HBsAg according to any one of claims 1 to 12, said amount being effective to induce an immune response to said variant HBV.

16. (canceled).

17. (withdrawn) Use of a variant HBV or an HBsAg from said variant HBV in screening for an agent useful in the treatment or prophylaxis of infection by said variant HBV.